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# Reply to Tasker and to Lellouche and L'Her

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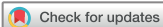
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## Reply to Tasker and to Lellouche and L'Her

From the Authors:

Professor Tasker queries whether patients undergoing brainstem death testing could bias the association between exposure to hyperoxemia and mortality in our recent study (1). In our database, these patients represent a tiny fraction of patients evaluated. For the Days 1, 3, 5, and 7 cohorts, there were only 33 (0.1%), 14 (0.1%), 9 (0.1%), and 6 (0.1%) patients, respectively, in whom there was semantic labeling for death confirmed using neurological criteria. Owing to these low numbers, we did not attempt to stratify by this variable. This is likely to be a small underestimate of patients exposed to apnea testing, because this label refers only to patients who met full criteria rather than to patients who underwent brainstem death testing itself, though it is standard practice in the United Kingdom not to proceed with testing unless there is good evidence that the result is likely to be positive. A sensitivity analysis, however, confirms that our original findings are robust even after exclusion of these patients.

We respectfully disagree that the study implies an “all-or-nothing” effect. The Royston method for evaluating exposures with a spike at zero is designed to introduce a discontinuity in a continuous variable at zero. Both indicator and dose components must be considered simultaneously. By analogy to cigarette exposure, this would be akin to suggesting that smoking is associated with harm, but we are unclear whether smoking 20 cigarettes per day is worse than smoking 10. The statistical power to demonstrate the dose-independent effect is much higher than the dose-dependent effect.

L'Her and Lellouche request summary distribution measures of  $\text{PaO}_2$ . Concerning the study variable of interest (i.e., “hyperoxemia dose,” samples with  $\text{PaO}_2 \geq 13.3$  kPa), the median was 15.8 kPa, and the 5%, 25%, 75%, and 95% centiles were 13.5, 14.3, 18.9, and 30.5 kPa, respectively. This is a right-skewed distribution, as one would expect after censoring values  $< 13.3$  kPa. Regardless, we challenge their assertion that “[i]f the range of  $\text{PaO}_2$  values is too narrow, no dose–effect relationship can be established.” The effect of interest was cumulative exposure, so even minor deviations of the underlying  $\text{PaO}_2$  would thus aggregate and become apparent over time. Notwithstanding this, there was good variability in the raw data that informed the creation of the “hyperoxemia dose” variable.

Our approach was clear in that we were trying to create an unambiguous definition of oxygen excess rather than attempting to establish an optimal level for  $\text{PaO}_2$ . The paper by Helmerhorst and colleagues (2) that L'Her and Lellouche cited did not, in our view, account for inherent confounding from treatment–physiology interactions; the optimal  $\text{PaO}_2$  they reported should be viewed with a degree of healthy skepticism. We believe that questions regarding optimal  $\text{PaO}_2$  and the importance of balancing this against prevention of significant hypoxemia remain unanswered. Although there is mounting evidence of the harm associated with excess oxygen exposure, there remains a lack of strong causal evidence. We advocate for well-powered randomized controlled trials to help elucidate these important questions. ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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